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EXAMINER	
BERTAGNA, ANGELA MARIE	
ART UNIT	PAPER NUMBER
1637	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/24/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/730,479	SORGE ET AL.	
	Examiner	Art Unit	
	Angela Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-57* is/are pending in the application.

4a) Of the above claim(s) *41-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 November 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/5/03; 7/22/04; 6/30/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1-40 in the reply filed on October 30, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 41-57 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on October 30, 2006.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Drawings

2. The drawings were received on November 8, 2004. These drawings are objected to, because they are not labeled "Replacement Sheet" as required by 37 C.F.R. 1.121(d). Appropriate correction is required.

Claim Interpretation

3. Claims 1, 5, 21, and 25 recite that the probes bind the target nucleic acid in "close proximity" to one another. Absent a specific limiting definition in the specification (only examples are presented) any distance between the two probes hybridized to the target may be properly considered "close proximity".

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8 and 40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8 and 40 recite the limitation "said probe binding". There is insufficient antecedent basis for this limitation in the claim. It appears that "said probe binding sequence" was intended.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-8 13, 17, 18, 20-27, 32, 33, 36, 37, 39, and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Urdea et al. (US 5,681,697).

Regarding claim 1, Urdea teaches a composition comprising: (1) a polynucleotide target; (2) a first target-hybridizing probe which comprises a target binding sequence (P1-DNA) which hybridizes to a strand of said target polynucleotide and a probe binding sequence (P1-P); and (3) a second target-hybridizing probe which comprises a target binding sequence (P2-DNA) which hybridizes, in close proximity, to said strand of said target polynucleotide and a probe binding sequence (P2-P) (see Figures 12 & 13 and column 15, line 50 – column 16, line 32, where the label extender probes (LE1 and LE2) bind the target nucleic acid via their target-specific portions in close proximity to one another. The LE1 and LE2 probes also contain probe-binding regions non-complementary to the target.).

Regarding claim 2, Urdea teaches that the composition of claim 1 further comprises a non-target-hybridizing probe 3 labeled with label A and a non-target-hybridizing probe 4 labeled with label B, wherein said probe 3 hybridize to said P1-P sequence and said probe 4 hybridizes to said P2-P sequence (see Figures 12 and 13, where Urdea teaches differently labeled AMP1 and AMP2 probes that hybridize to the non-target binding portions of the LE1 and LE2 probes; see column 15, line 50 – column 16, line 32 for further description of the Figures).

Regarding claim 3, Urdea teaches that label A interacts with label B to generate a signal indicative of an amount of said target polynucleotide (column 16, lines 15-32).

Regarding claim 4, Urdea teaches a composition (see Figures 12 and 13) comprising: (1) a target polynucleotide (see Figure 12)

(2) a first target-hybridizing probe comprises a target binding sequence (P1-DNA) which is complementary to a first sequence on a strand of said target polynucleotide and a probe-binding sequence (P1-P) (Figure 12 – the LE1 probe discussed above)

(3) a second target-hybridizing probe comprises a target binding sequence (P2-DNA) which is complementary to a second sequence on said strand of said target polynucleotide and a probe-binding sequence (P2-P) (Figure 12 – the LE2 probe discussed above)

(4) a non-target-hybridizing probe 3 labeled with label A (Figure 12, the AMP1 probe)

(5) a non-target-hybridizing probe 4 labeled with label B (Figure 12, the AMP2 probe),

wherein said P1-P sequence is complementary to probe 3 and said P2-P sequence is complementary to probe 4 (see Figure 12), and said label A interacts with said label B to generate a signal indicative of an amount of said target polynucleotide (see Figure 12 and column 16, lines 15-32).

Regarding claim 5, Urdea teaches that the first target-hybridizing probe and said second target-hybridizing probe hybridize to a same strand of said target polynucleotide in close proximity (see Figures 12 & 13 and column 15, lines 50-65).

Regarding claim 6, Urdea teaches that probe 3 hybridizes to said P1-P sequence and said probe 4 hybridizes to said P2-P sequence (see Figure 12, where the AMP1 probe (corresponding to the instant probe 3) hybridizes to the probe-binding sequence (P1-P) on the LE1 probe and the AMP2 probe (corresponding to the instant probe 4) hybridizes to the probe-binding sequence (P2-P) on the LE2 probe).

Regarding claim 7, Urdea teaches that label A and label B are members of a pair of interactive labels (column 16, lines 15-32).

Regarding claim 8, Urdea does not explicitly state that the 5' portion of probe 1 and the 3' portion of probe 2 contain the target-binding portion. However, this is inherent from Figure 12. In this figure if the target sequence is depicted 3' – 5' from left to right, LE1 (corresponding to probe 1) has a target-binding sequence in the 5' portion of the molecule, and LE2 (corresponding to probe 2) has a target binding sequence in the 3' portion of the molecule. This also holds if the situation is reversed (i.e. the target is depicted 5'-3' from left to right), because the designation of probe 1 and probe 2 is arbitrary. That is, if the target is depicted 5'-3' from left to right, LE1 and LE2 of Urdea correspond to the instant probes 2 and 1, respectively.

Regarding claim 13, Urdea teaches that probes 3 and 4 (AMP1 and AMP2 in Figure 12) share no homology to any polynucleotide isolated from a sample containing said target polynucleotide (see column 15, lines 50-65, where Urdea teaches that the AMP1 and AMP2 probes only hybridize to the LE1 and LE2 probes, respectively).

Regarding claim 17, probes 3 and 4 (AMP1 and AMP2 probes) of Urdea inherently have a higher Tm than the P1-DNA and P2-DNA sequences. Urdea teaches P1-DNA and P2-DNA sequences of at most 53 nucleotides (see the label extender probes recited in Examples I and II at columns 18 and 23, which contain sequences corresponding to the P1-DNA and P2-DNA sequence). The AMP probes (which correspond to the instant probes 3 and 4) taught by Urdea are much longer (see columns 19-20, where the amplifier probe resulting from ligation of the comb body shown in column 19, lines 54-60 and the sidechain (SEQ ID NO: 21) shown at column 20, lines 48-49, results in a probe 186 nucleotides in length). Therefore, the third and fourth probes taught by Urdea inherently have a greater melting temperature than the P1-DNA and P2-DNA sequence present in the label extender probes of Urdea. Moreover, Urdea also

teaches that amplification multimer probe (corresponding to the instant probes 3 and 4) has a higher stability (Tm) compared to the label extender probes (i.e. the P1-DNA and P2-DNA sequences) (see column 15, lines 8-27).

Regarding claim 18, Urdea teaches that the composition of claims 1 or 4 may be used in a PCR method (column 12, lines 50-55). PCR inherently requires a forward and a reverse primer for the amplification of said target polynucleotide.

Regarding claim 20, Urdea teaches that the composition of claims 1 or 4 further comprises a control polynucleotide (column 24, lines 46-56, where the salmon sperm DNA is a control polynucleotide).

Regarding claims 21-27, 32, 33, 36, 37, 39, and 40, Urdea teaches kits comprising the compositions recited in claims 1-8, 13, 17, 18, and 20 (see claim 5, the abstract, and column 4, lines 34-36).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 9, 10, 14, 28, 29, and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Urdea et al. (US 5,681,697) in view of Zamecnik et al. (WO 92/14845 A1).

Urdea teaches the composition and kit of claims 8 and 27, as discussed above.

Urdea does not teach that the third and fourth probes are fluorescently labeled to permit FRET detection.

Zamecnik teaches a method of detecting nucleic acids based on fluorescence energy transfer (FRET).

Regarding claims 9, 10, 28, and 29, Zamecnik teaches hybridization of two oligonucleotide probes, one labeled with a donor fluorophore (fluorescein) and the other labeled with an acceptor fluorophore (rhodamine), to a target nucleic acid. Hybridization of both probes in close proximity to one another on the target sequence results in FRET (due to energy transfer between the donor and acceptor fluorophore) and an observable fluorescence signal (see abstract and pages 3-4 for a general description).

Regarding claims 14 and 33, Zamecnik teaches that the fluorophores may be attached to either the 3' or 5' end of the probes (page 11, line 30 – page 12, line 1). Zamecnik particularly points out the location of the fluorophore in the probe is not critical so long as the fluorophores

are close enough when hybridized to the target to generate an observable fluorescence signal and not so close as to encounter problems with steric hindrance (page 12, lines 1-16).

Zamecnik teaches that FRET detection eliminates the need for separation of hybridized and unhybridized probe molecules, and therefore burdensome immobilization and washing steps are unnecessary. Zamecnik also teaches that FRET detection does not require use of a solid support for target immobilization, and therefore, the common problem of nonspecific binding between detection probes and the solid support is eliminated (see page 5, lines 13-32).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to substitute FRET detection probes for enzyme-based detection probes in the composition taught by Urdea. An ordinary practitioner would have been motivated to do so, because Zamecnik expressly taught that FRET probes eliminated the need to perform burdensome target immobilization and washing steps required when using the enzyme-labeled probes taught by Urdea to detect nucleic acids. An ordinary practitioner would have recognized that by avoiding immobilization and washing steps, nucleic acid detection would be simpler and more efficient. An ordinary practitioner would also have been motivated by the teachings of Zamecnik to substitute FRET probes for enzyme-labeled probes in order to eliminate the problem of nonspecific hybridization between the detection (amplifier) probes and the solid support used for target immobilization. Finally, regarding the location of the fluorophores in the probes, an ordinary practitioner would have been motivated to incorporate the fluorophores in any location that maximized the observable FRET signal while avoiding steric hindrance, such as the 5' end of the fourth probe and the 3' end of the third probe, for example. Therefore, an ordinary user of the probe composition taught by Urdea, interested in eliminating the

requirement for target immobilization and washing, would have been motivated to substitute FRET detection probes, as taught by Zamecnik, for the enzyme-labeled probes taught by Urdea, thus resulting in the instantly claimed compositions and kits.

8. Claims 11, 12, 30, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Urdea et al. (US 5,681,697) in view of Zamecnik et al. (WO 92/14845 A1) and further in view of Nazarenko et al. (US 5,866,336).

The combined teachings of Urdea and Zamecnik result in the composition of claim 10 and the kit of claim 29, as discussed above.

Zamecnik teaches a fluorescein/rhodamine FRET pair (page 8, lines 13-16), but does not teach the claimed FAM/ROX pair. Also, Zamecnik does not teach the use of a dark quencher as the acceptor molecule.

Nazarenko teaches FRET probes for the detection of nucleic acids (see abstract).

Regarding claims 11 and 30, Nazarenko teaches the use of a FAM/ROX FRET pair (see Table 1 in columns 17-18 and also column 18, lines 29-35). Regarding the choice of a FRET pair, Nazarenko stated, "One of ordinary skill in the art can easily determine, using art-known techniques of spectrophotometry, which fluorophores will make suitable donor-acceptor FRET pairs. For example, FAM (which has an emission maximum of 525 nm) is a suitable donor for TAMRA, ROX, and R6G (all of which have an excitation maximum of 514 nm) in a FRET pair (column 18, lines 29-35)."

Regarding claims 12 and 31, Nazarenko teaches that the acceptor is a dark quencher, specifically DABCYL (see, for example, column 39, lines 1-21, where Nazarenko teaches a

hairpin probe comprising a FAM label on the 3' terminus and a DABCYL label on the 5' terminus). Regarding the use of DABCYL as an acceptor, Nazarenko stated, "As a quencher, however, DABCYL has an advantage of being a non-fluorescent chromophore: it absorbs the energy of the fluorescein without emitting light itself. As a result, the emission of the fluorescein may be detected more precisely, without interference from the emission of the acceptor (column 39, lines 58-64)."

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to use a FAM/ROX FRET pair or a FAM/DABCYL FRET pair in the probe composition resulting from the combined teachings of Urdea and Zamecnik. An ordinary practitioner would have been motivated to use a FAM/ROX pair, because Nazarenko expressly taught that this pair was useful for nucleic acid detection (see Table 1 in columns 17-18 and column 18, lines 29-35 cited above). Moreover, since Nazarenko taught numerous equivalent FRET pairs, including the fluorescein/rhodamine pair taught by Zamecnik (see Table 1 in columns 17-18), an ordinary practitioner would have expected a reasonable level of success in substituting different FRET pairs in the composition as desired. An ordinary practitioner also would have been motivated to substitute DABCYL as the acceptor molecule in the composition resulting from the combined teachings of Urdea and Zamecnik, because Nazarenko taught that DABCYL absorbed the energy of the fluorescein donor without emitting light itself, thereby permitting more precise measurement of fluorescence emission (column 39, lines 58-64). Therefore, an ordinary user of the composition resulting from the combined teachings of Urdea and Zamecnik, interested in obtaining additional equivalent FRET pairs and/or more precise emission measurements, would have been motivated to substitute either a FAM/ROX pair or a

FAM/DABCYL pair for the fluorescein/rhodamine pair taught by Zamecnik, as suggested by Nazarenko, thus resulting in the claimed compositions and kits.

9. Claims 15, 16, 34, and 35 are rejected under 35 U.C.C. 103(a) as being unpatentable over Urdea et al. (US 5,681,697) in view of Gelfand et al. (US 5,804,375).

Urdea teaches the composition of claim 4 and the kit of claim 24, as discussed above.

Urdea does not teach modification of the 3' terminus of a probe with a phosphate group to prevent extension.

Gelfand teaches a method for detection of nucleic acids during an amplification reaction using an oligonucleotide probe (see column 2, line 50 – column 3, line 16 for a general description).

Regarding claims 15, 16, 34, and 35, Gelfand teaches phosphorylation of the 3' terminus of the probe to prevent incorporation of the probe into a primer extension product (column 7, lines 33-40).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to phosphorylate the 3' terminus of the detection probes taught by Urdea. Urdea taught using the labeled detection probes to detect amplification products (column 12, lines 50-55). An ordinary practitioner would have been motivated by the teachings of Gelfand to phosphorylate the 3' terminus of the detection probes (AMP1 and AMP2) in order to prevent undesirable polymerase extension of these probes during the amplification reaction. Therefore, the compositions and kits of the instant claims 15, 16, 34, and 35 are obvious in view of the combined teachings of Urdea and Gelfand.

10. Claims 19 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Urdea et al. (US 5,681,697) in view of Andrus et al. (WO 02/083927 A2). The Andrus reference obtains benefit of Provisional Application No. 60/284,334, filed April 17, 2001.

Urdea teaches the composition of claim 18 and the kit of claim 37, as discussed above.

Urdea teaches PCR amplification (which inherently requires a forward and reverse primer) prior to detection (column 12, lines 50-55), but does not teach asymmetric amplification using a five-fold excess of one primer.

Andrus teaches methods for detection of nucleic acids comprising PCR amplification followed by probe hybridization (see pages 13-14 for a general description).

Regarding claims 19 and 38, Andrus teaches asymmetric amplification using a primer ratio of 1:5, where the primer (forward or reverse) used to synthesize the strand complementary to the detection probe is present in excess (page 16, lines 7-12). Andrus states, "In particular, for improved sensitivity, the primer whose nucleotide sequence makes up part of the probe sequence is provided in a lower concentration in the sample as compared with the other primer. 'Asymmetric concentrations' of primers are particularly preferred if the probe sequences 'hybridize asymmetrically' with the additional amplification products; or hybridize exclusively with the segment of the additional amplification products that is complementary to a primer (page 15, line 30 – page 16, line 6)."

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to include in the composition of Urdea forward and reverse primers in asymmetric amounts, specifically, with an excess of the primer that generates the sequence complementary to the first and second probes. An ordinary practitioner would have been motivated to do so,

because Andrus expressly taught that the use of such an excess improved detection sensitivity (page 15, line 30 – page 16, line 6). An ordinary practitioner also would have been motivated to use a fivefold excess of the forward or reverse primer since this ratio was specifically taught by Andrus (page 16, lines 7-12). Therefore, an ordinary user of the composition taught by Urdea, interested in improving the detection sensitivity when using PCR products as the target nucleic acid, would have been motivated to use an asymmetric ratio of primers, such as 1:5, as suggested by Andrus, thus resulting in the instantly claimed composition and kit.

Conclusion

No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela Bertagna whose telephone number is 571-272-8291. The examiner can normally be reached on M-F, 7:30 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Angela Bertagna
Examiner, Art Unit 1637
January 18, 2007

amb

JEFFREY FREDMAN
PRIMARY EXAMINER
1/19/07